Evidence for DNA-mediated nuclear compartmentalization distinct from phase separation.

Journal: Elife

Publication Year: 2019

Authors: David Trombley McSwiggen, Anders S Hansen, Sheila S Teves, Herve Marie-Nelly, Yvonne Hao, Alec Basil Heckert, Kayla K Umemoto, Claire Dugast-Darzacq, Robert Tjian, Xavier Darzacq

PubMed link: 31038454

Funding Grants: Single Molecule Biophysics and Biology of Cellular Identity

Public Summary:
RNA Polymerase II (Pol II) and transcription factors form concentrated hubs in cells via multivalent protein-protein interactions, often mediated by proteins with intrinsically disordered regions. During Herpes Simplex Virus infection, viral replication compartments (RCs) efficiently enrich host Pol II into membraneless domains, reminiscent of liquid-liquid phase separation. Despite sharing several properties with phase-separated condensates, we show that RCs operate via a distinct mechanism wherein unrestricted nonspecific protein-DNA interactions efficiently outcompete host chromatin, profoundly influencing the way DNA-binding proteins explore RCs. We find that the viral genome remains largely nucleosome-free, and this increase in accessibility allows Pol II and other DNA-binding proteins to repeatedly visit nearby DNA binding sites. This anisotropic behavior creates local accumulations of protein factors despite their unrestricted diffusion across RC boundaries. Our results reveal underappreciated consequences of nonspecific DNA binding in shaping gene activity, and suggest additional roles for chromatin in modulating nuclear function and organization.

Scientific Abstract:
RNA Polymerase II (Pol II) and transcription factors form concentrated hubs in cells via multivalent protein-protein interactions, often mediated by proteins with intrinsically disordered regions. During Herpes Simplex Virus infection, viral replication compartments (RCs) efficiently enrich host Pol II into membraneless domains, reminiscent of liquid-liquid phase separation. Despite sharing several properties with phase-separated condensates, we show that RCs operate via a distinct mechanism wherein unrestricted nonspecific protein-DNA interactions efficiently outcompete host chromatin, profoundly influencing the way DNA-binding proteins explore RCs. We find that the viral genome remains largely nucleosome-free, and this increase in accessibility allows Pol II and other DNA-binding proteins to repeatedly visit nearby DNA binding sites. This anisotropic behavior creates local accumulations of protein factors despite their unrestricted diffusion across RC boundaries. Our results reveal underappreciated consequences of nonspecific DNA binding in shaping gene activity, and suggest additional roles for chromatin in modulating nuclear function and organization.